

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 October 2001 (04.10.2001)

PCT

(10) International Publication Number
WO 01/72288 A2

(51) International Patent Classification⁷: **A61K 31/00**

d'Asturies, 35, E-08034 Barcelona (ES). ORTIZ, José A.
[ES/ES]; Còrsega, 429m, E-08037 Barcelona (ES).

(21) International Application Number: **PCT/EP01/03536**

(74) Agents: KINZEBACH, Werner et al.; Reitstötter, Kinzebach & Partner, Sternwartstr. 4, 81679 München (DE).

(22) International Filing Date: 28 March 2001 (28.03.2001)

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(30) Priority Data:
P2000 00765 29 March 2000 (29.03.2000) ES

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

Published:

(75) Inventors/Applicants (*for US only*): FOGUET, Rafael [ES/ES]; Lluçanès, 8, E-08028 Barcelona (ES). RAMENTOL, Jorge [ES/ES]; Lleó XIII 2, E-08022 Barcelona (ES). LOZANO, Rafael [ES/ES]; Bertran 45, E-08023 Barcelona (ES). AGUT, Julián [ES/ES]; Riera 13E, E-08190 Sant Cugat (ES). TORRES, Jesús [ES/ES]; Ptg. Forasté 4bis, E-08017 Barcelona (ES). RAGA, Manuel M. [ES/ES]; Sors 17-21, E-08024 Barcelona (ES). CASTELLÓ, Josep M. [ES/ES]; Av. Príncep

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/72288 A2

(54) Title: USE OF CDP-CHOLINE FOR THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME

(57) Abstract: The invention relates to the use of CDP-Choline or its pharmaceutically acceptable salts for the preparation of a medicinal product for the treatment of alcohol withdrawal syndrome at daily doses equivalent to 0.5-2g of free CDP-Choline.

USE OF CDP-CHOLINE FOR THE TREATMENT OF ALCOHOL WITHDRAWALSYNDROMEDESCRIPTION

The present invention relates to the use of CDP-choline for the treatment of alcohol withdrawal syndrome.

The toxic effects of alcohol on central nervous system are basically exerted on neuronal membrane and synapses (Leonard B. E., *Alcohol Alcohol.*, 1986: 21(4), 325-338).

Histological alterations of neuronal structure consist in a lesser branching of hippocampus nerve cells and Purkinje's cells. Comparison of brains from healthy subjects with those from alcoholic patients revealed a lesser branching of pyramidal neuronal basal dendrites in upper cerebral cortex and motor cortex (Ledit M. and Mandel P., *M S-Medecine Sciences*, 1988: 4(6), 352-357).

Chronic alcohol abuse has also been reported to impair dopamine receptor sensitivity. This effect is probably related to changes in neuronal membrane fluidity and in the number and functionality of receptors, as well as to a decrease in acetylcholine reuptake and dopamine deficiency (Carlen P. L. and col., *Ann. Neurol.*, 1981: 9(1), 84-86).

CDP-choline (cytidine diphosphate choline, Citicoline) is a key intermediate in the synthesis of structural phospholipids present in the neuronal membrane (Kennedy E. P. and Weiss S. B., *J. Biol. Chem.*, 1956; 222, 193-214) and plays an important role in its formation and repair when the phospholipidic structure is damaged by endogenous or exogenous causes involving a decrease in cytidine and choline uptake.

The administration of CDP-choline enhances dopamine synthesis and release (Martinet M. et al., *Biochem. Pharmacol.*, 1981; 30(5), 539-541) as well as choline and acetylcholine brain levels. The administration of repeated doses of CDP-choline produces an increase of brain phospholipid levels, which is secondary to an increase of cytidine and choline plasma levels (Agut J. et al., *Ann. New York Acad. Sci.*, 1993; 695, 318-320).

Surprisingly, the applicants have found out that the administration of CDP-choline to alcoholic patients reduces the duration and intensity of their withdrawal symptoms and induces an evident recovery in a significant proportion of patients.

The use of CDP-choline according to the present invention, which includes a method for treating alcohol withdrawal syndrome, comprises the administration of an effective

amount of CDP-choline or a pharmaceutically acceptable salt thereof to an alcoholic patient.

According to the present invention, CDP-choline is administered as free compound or as a pharmaceutically acceptable salt, whether in anhydrous or hydrated form, conveniently mixed with pharmaceutical carriers and/or excipients, to humans at daily doses of 0.5 to 2 g inclusive in free CDP-choline, preferably from 0.5 to 1 g inclusive, both orally and parentally. Pharmaceutically acceptable salts of CDP-choline include its alkaline or alkaline earth salts, such as its sodium, potassium, calcium and magnesium salts or its acid addition salts with a mineral or organic acid, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, citric acid, lactic acid, malonic acid, tartaric acid, acrylic acid, metacrylic acid, malic acid, maleic acid, fumaric acid, benzoic acid, salicylic acid, cinnamic acid, methane sulphonic acid, benzenesulphonic acid, p-toluensulphonic acid and nicotinic acid.

CDP-choline and its salts, whether as anhydrous or hydrated substances, under the invention may be administered orally in the form of tablets, capsules, powder, granules, cachets, lozenges, solution, suspension, emulsion, syrup, gel and the like; or parenterally in the form of solution,

suspension, emulsion or the like for intravenous or intramuscular injection.

EXAMPLES

The present invention is illustrated by the Examples that follow. Those skilled in the art will be able to make any change provided the specific embodiment of the invention is not modified and, therefore, the invention is not limited to the specific details of the Examples.

EXAMPLE 1: 500 mg tablets

CDP-choline, sodium salt	522.5 mg
Talc	30.0 mg
Magnesium stearate	3.0 mg
Silicon dioxide	2.5 mg
Croscarmellose sodium	20.0 mg
Corn starch	20.0 mg
Microcrystalline cellulose s.q.	780.0 mg

EXAMPLE: 25% oral solution

CDP-choline, sodium salt	26.12 g
70% Sorbitol	20.00 g
Methyl p-hydroxybenzoate	0.16 g

Propyl p-hydroxybenzoate	0.04 g
Disodium citrate	0.60 g
Saccharin sodium	0.02 g
Strawberry essence	0.04 g
Red Punzo 4R	0.50 mg
Anhydrous citric acid	0.05 g
Purified water s.q.	100.00 ml

EXAMPLE 3: Solution for injection

CDP-choline, sodium salt	522.50 mg
Hydrochloric acid, pH 6.0-6.5 s.q.	
Water for injection s.q.	4.00 ml

EXAMPLE 4 : Open clinical study of CDP-choline in alcohol withdrawal syndrome

The progress of alcohol withdrawal syndrome was assessed in an open study conducted in 197 patients. CDP-choline was administered at doses of 500 mg/d i.m. or 600 mg/d p.o. for 60 days. At 30 and 60 days following treatment, significant differences ($p<0.001$) were observed in the assessments performed. At 60 days, 55.83% of patients had given up drinking alcohol and 31.97% of patients drank much less. A significant improvement was observed on anxiety, tremor, disorientation, insomnia, dysarthria, tendency to suicide and neuritic pains.

EXAMPLE 5: Open, randomized, comparative clinical study of CDP-choline in alcohol withdrawal syndrome versus clomethiazole and vitamin B.

An open, randomized and comparative study on the conventional therapy of alcohol withdrawal syndrome was conducted in 40 patients. Patients were randomly distributed in two groups of 20. One of the groups was used as control and received clomethiazole and vitamin B₁, B₆ and B₁₂. This treatment regimen was maintained for 8 days, and then patients were given diazepam until completion of treatment (60 days). The other group of patients received the same treatment regimen plus CDP-choline 500 mg i.m. every 12 h for the first 30 days and CDP-choline 200 mg i.m. every 8 h for the remaining 30 days. The patients who received CDP-choline plus the conventional therapy showed significant differences versus control at 30 days following treatment in tremor incidence ($p<0.05$), cramps ($p<0.05$), asthenia ($p<0.05$), emotional lability ($p<0.01$), nervousness ($p<0.05$) and social withdrawal ($p<0.05$).

CLAIMS

1. The use of CDP-choline or of a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of alcohol withdrawal syndrome.

2. The use according to claim 1 in which the pharmaceutically acceptable salts of CDP-choline are its alkaline or alkaline earth salts or its salts with mineral or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, citric acid, lactic acid, malonic acid, tartaric acid, acrylic acid, metacrylic acid, maleic acid, maleic acid, fumaric acid, benzoic acid, salicylic acid, cinnamic acid, methane sulphonic acid, benzenesulphonic acid, p-toluensulphonic acid and nicotinic acid, in anhydrous or hydrated form.

3. The use according to claims 1 or 2 at daily dose: in equivalent amounts of free CDP-choline ranging from 0.1 to 2 g.

4. The use according to claim 3, wherein the dose: range from 0.5 to 1 g.

5. A method for the treatment of alcohol withdrawal syndrome comprising administering to an alcoholic patient in need thereof an effective amount of CDP-choline or of a pharmaceutically acceptable salt thereof.